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(21) International Application Number: PCT/IE96/00086 (22) International Filing Date: 13 December 1996 (13.12.96) (30) Priority Data: 950940 13 December 1995 (13.12.95) IE (71) Applicant (for all designated States except US): DULLATUR LIMITED [IE/IE]; 1 Stokes Place, Dublin 2 (IE). (72) Inventors; and (75) Inventors/Applicants (for US only): BYRNE, William [IE/IE]; 6 Mather Road North, Mount Merrion, County Dublin (IE). O'DRISCOLL, Caitriona, M. [IE/IE]; 10 Grosvenor Place, Rathmines, Dublin 6 (IE). CORRIGAN, Owen, I. [IE/IE]; 10 Asgard Park, Howth, County Dublin (IE). (74) Agents: O'CONNOR, Donal, H. et al.; Cruickshank & Co., 1 Holles Street, Dublin 2 (IE).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DE (Utility model), DK, DK (Utility model), EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: A CALCITONIN PREPARATION (57) Abstract An oral calcitonin preparation includes an absorption enhancer and, optionally, a protease enzyme inhibitor. The enzyme inhibitor is selected from aprotinin, potato carboxypeptidase inhibitor and chymostatin. The enhancer may be a bile acid or salt thereof, especially sodium glycocholate, sodium cholate or sodium deoxycholate. Alternatively the enhancer may be a non-ionic surfactant, preferably a polyoxyethyleneglyceroltricitricinoleat derivative. The enhancer may also be a cyclodextrin or its derivatives such as a hydroxypropylbetacyclodextrin.		

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"A Calcitonin Preparation"

The invention relates to a calcitonin preparation.

Calcitonins are medicaments which are particularly useful in achieving a hypocalcemic effect. Calcitonin lowers blood calcium levels by increasing urinary calcium excretion and inhibiting bone resorption. It is used therapeutically to treat osteoporosis, Padgett's disease and hypercalcemias.

There are major problems to be overcome to achieve the successful delivery of calcitonins. The problems include degradation of the drug by various proteolytic enzymes and poor permeability through lipoidal mucous membranes due to the non-lipophilic nature of calcitonins. Consequently, the major route of administration of calcitonins to date has been by parenteral injection producing a number of gastric and vascular side effect. In addition, the biological half-lives of calcitonins are very short and frequent administration is required to maintain activity. If calcitonins are to be widely used in the future non parenteral routes of administration, which allow self-medication and enhance patient compliance, must be developed.

Several alternative non parenteral routes of administration for calcitonins including: oral, nasal, vaginal, rectal, buccal and pulmonary have been investigated with varying degrees of success. The nasal route is better tolerated than the parenteral route however, local nasal irritation is common. The oral route, however, is the preferred route as it is the safest, most convenient and most widely acceptable to the patient. In addition, the intestinal tract is intended for absorption in contrast to other routes such as the

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nasal route. Using other routes than oral for prolonged administration might therefore induce unpredictable side effects. To date however, attempts to achieve oral delivery of calcitonins have not been entirely successful.

- 5 The object of the invention therefore is to provide an oral dosage form for calcitonins.

According to the invention, there is provided an oral calcitonin preparation comprising:-

a calcitonin; and

- 10 an absorption enhancer.

In one embodiment of the invention, the preparation includes an enzyme inhibitor, especially a protease enzyme inhibitor. The inhibitor is preferably selected from one or more of aprotinin, potato carboxypeptidase inhibitor and chymostatin. Most preferably the inhibitor is or
15 includes potato carboxypeptidase.

In one embodiment of the invention the absorption enhancer is selected from at least one bile acid with the basic bile acid structure including glycocholic, taurocholic, chenodeoxycholic, ursodeoxycholic, deoxycholic and cholic
20 acids.

In another embodiment of the invention the enhancer alternatively or additionally is a non ionic surfactant, preferably a polyoxyethylene-glyceroltriricinoleat derivative, especially Cremophor EL (Trade Mark of BASF).
25

In a further embodiment of the invention the enhancer alternatively or additionally is a cyclodextrin or its derivatives such as hydroxypropylbetacyclodextrins (HPBCD).

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In a preferred embodiment of the invention, the bile acid salt is an alkali metal salt, preferably a sodium salt.

Preferably, the enhancer is sodium glycocholate, sodium cholate and/or sodium deoxycholate.

- 5 Preferably the calcitonin is salmon calcitonin or human calcitonin.

In a particularly preferred embodiment, the oral calcitonin preparation comprises:-

10 a calcitonin, preferably salmon calcitonin or human calcitonin,

sodium glycocholate, sodium cholate and/or sodium deoxycholate and

potato carboxypeptidase.

15 The preparation may be in a liquid form but is preferably in a solid form which is incorporated into a tablet or capsule. Typically the solid form is prepared by freeze drying with appropriate stabilising or lyoprotectants such as polyethyleneglycol e.g. PEG6000, sugars including glucose, lactose, trehalose, and/or mannitol. The
20 preparation preferably also includes pH regulator(s).

25 The term "calcitonin" includes calcitonins which are naturally occurring (whether extracted or produced synthetically) and derivatives and analogues (including those involving non-peptide linkages) having a hypocalcemic effect or calcitonin-like activity. In particular calcitonins include salmon calcitonin and human calcitonin.

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The term "bile acid" embraces all bile acids with the basic bile acid structure, both conjugated and unconjugated, and includes glycocholic, taurocholic, chenodeoxycholic, ursodeoxycholic, deoxycholic and cholic acids. Pharmacologically acceptable salts of such acids are also included, particularly alkali metal salts, especially sodium salts.

The invention will be more clearly understood from the following description thereof given by way of example only.

We have discovered that the bile salt sodium glycocholate (NaGLY) sodium cholate and sodium deoxycholate not only enhance the intestinal absorption of salmon calcitonin (sCT) with a resultant increase in hypocalcemic effect, but also delays/prevents degradation. Further, the inclusion of a range of protease enzyme inhibitors including aprotinin, potato carboxypeptidase inhibitor (pCPI) and chymostatin have a synergistic effect on the effects of these bile acid salts.

1. Intestinal Stability

In-vitro stability studies investigating the stability of sCT in rat gut homogenate have been undertaken. The effects of NaGLY and a range of protease inhibitors on the degradation of sCT in rat intestinal homogenate after 10 minutes exposure at pH 7.4 and 4.2 are shown in Table 1.

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Table 1: The effects of a range of protease inhibitors on the degradation of sCT in rat intestinal homogenate after 10 minutes exposure in pH 7.4 and pH 4.2.

	Inhibitor	Type	% Inhibition pH	% Inhibition pH
			7.4	4.2
5	18.8 uM Trypsin/Chymotrypsin	serine protease	16.4	0.5
	200 uM Phosphoramidon	metal protease	17.6	-0.1
10	0.5 mg/ml Aprotinin	serine protease	43.8	2.8
	200 uM TLCK	papain and trypsin	-7.8	2.6
	15 nM NaGlycocholate		70.0	8.1
	200 uM pCPI	carboxypeptidase	75.8	4.7
15	2mM N-Ethylmaleimide	sulfahydryl agent	-21.1	6.5
	200 uM 1.10-Phenanthroline	chelator	-34.1	6.5
	2 mM Chymostatin	serine protease	53.7	ND
20	500 uM Pepstatin A	aspartic protease	2.4	ND
	2 mM Bacitracin	aminopeptidase	-30.6	ND

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Maximum protection against degradation was obtained in the presence of NaGLY, pCPI, chymostatin and aprotinin. Combinations of NaGLY with various enzyme inhibitors produced synergistic effects and resulted in further protection against degradation as outlined in Table 2.

TABLE 2

Synergistic effect of protease inhibitors on the degradation of sCT in rat intestinal homogenate after 20 minutes exposure in pH 7.4 and pH 6.5.

10	INHIBITOR	% INHIBITION pH 7.4	% INHIBITION pH 6.5
	15 mM NaGlycocholate	83.3	86.2
	0.5 mg/ml Aprotinin		28.9
	200 uM pCPI	73.3	82.8
	NaGly/Aprotinin		87.9
15	NaGly./pCPI	88.2	90.1
	pCPI/Aprotinin		84.2
	NaGly./pCPI/Aprotinin		90.4

These results are plotted in Figures 1 and 2.

Protection of calcitonin against degradation in rat gut homogenate was also obtained with sodium cholate and sodium taurocholate as will be apparent from Figures 3 and 4.

2. Enzymatic activity in the upper versus lower gut

The enzymatic activity in the terminal ileum was also assessed by investigating the in-vitro stability of sCT in intestinal mucosal homogenate collected from this region. In the case of drug alone (sCT) significant degradation

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occurred, with less than 20% remaining after 30 min. The combination of NaGLY/pCPI significantly decreased the degradation of sCT in the lower region of the intestine as will be apparent from Figure 5.

- 5 The overall level of enzymatic activity in the intestine is lower in the lower regions of the gut. Consequently protection of the drug until it reaches, for example the colon, using technology that will be familiar to those skilled in the art, should further optimise the scope of
10 the delivery system of the invention.

3. Rat Intestinal Perfusion Model

In this model, two parameters have been monitored, in the absence and presence of enhancer:

- 15 (a) changes in sCT concentration in the intestinal perfusate with time and
- (b) changes in plasma calcium levels, as sCT produces a hypocalcemic effect this pharmacological response can be measured and used as an indication of sCT absorption.

- 20 In the presence of NaGLY a trend towards a decrease in steady state perfusate concentration of intact sCT relative to the control was observed (Figure 6). This decrease normally reflects enhanced absorption. Corresponding plasma calcium levels were determined
25 (Figure 7), relative to buffer alone and sCT alone. The presence of NaGLY resulted in an increase in pharmacological response as reflected in a decrease in calcium levels.

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The results suggest that a combination of specific protease enzyme inhibitors such as aprotinin, pCPI and chymostatin together with an enhancer such as NaGLY can increase the absorption and hence the bioavailability of sCT.

4. Pharmacological Response Data

Pharmacological response data obtained following intravenous (I.V.) bolus administration of sCT was used to construct a dose/response curve, Figure 8. This Figure shows the area above the intensity curve (AAIC) data, determined from plasma calcium data, as a function of sCT concentration. Calcium levels were also monitored after intraduodenal (I/D) perfusion of sCT alone, sCT/NaGLY, and sCT/NaGLY/pCPI and the appropriate AAIC values were calculated. Comparison of the I/D data with the I.V. dose response curve implies a two fold increase in drug permeability in the presence of the excipients. This increase in permeability is likely to increase in a whole animal model, as the contribution of pCPI will be more evident.

5. Additional support for increased membrane transport/absorption of sCT in the presence of absorption enhancers.

A human intestinal tissue culture model was also used to assess the transport of sCT. Enhanced transport was observed in the presence of the bile salts Na cholate, NaGLY, deoxycholate and taurocholate, the non-ionic surfactant Cremophor and cyclodextrin HPBCD. The data is given in Figures 9, 10 and 11.

6. Formulation

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The oral preparation may be in a liquid form but is preferably in a solid form which is incorporated into a tablet or capsule. Preparation of the solid form will typically involve freeze drying with appropriate
5 stabilising agents and/or lyoprotectants such as PEG6000, sugars including glucose, lactose, trehalose, and/or mannitol.

We have observed that the drug is subject to less degradation if the pH is maintained at from 3 to 6,
10 preferably approximately 4. For this purpose the formulation may include pH regulator(s) typically prepared from solid organic acids such as citric or tartaric or succinic acids and/or their salts, alone or in combination.

15 The oral formulation will therefore typically consist of:

Calcitonin
Absorption Enhancer
Protease Inhibitor
Lyoprotectant(s)
20 pH Regulator(s)

The solid formulation will typically be enclosed in a gelatin capsule or formulated as a tablet by techniques known in the art. The formulation will be pretreated with an enteric coating polymer. The enteric coating provides
25 protection of the drug against decomposition in the stomach and facilitates the release of the formulation components in the intestinal tract.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

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CLAIMS

1. An oral calcitonin preparation comprising:-

a calcitonin; and

an absorption enhancer.
- 5 2. A preparation as claimed in claim 1 including an enzyme inhibitor.
3. A preparation as claimed in claim 2 wherein the inhibitor is a protease enzyme inhibitor.
- 10 4. A preparation as claimed in claim 3 wherein the inhibitor is selected from one or more of aprotinin, potato carboxypeptidase inhibitor and chymostatin.
5. A preparation as claimed in any of claims 2 to 4 wherein the inhibitor is or includes potato carboxypeptidase inhibitor.
- 15 6. A preparation as claimed in any preceding claim wherein the absorption enhancer is at least one bile acid or salt thereof.
- 20 7. A preparation as claimed in claim 6 wherein the absorption enhancer is selected from bile acids with the basic bile acid structure both conjugated and unconjugated including glycocholic, taurocholic, chenodeoxycholic, ursodeoxycholic, deoxycholic and cholic acids.
- 25 8. A preparation as claimed in claim 6 or 7 wherein the bile acid salt is an alkali metal salt.

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9. A preparation as claimed in claim 8 wherein the alkali metal salt is a sodium salt.
10. A preparation as claimed in any preceding claim wherein the enhancer is or includes sodium glycocholate.
5
11. A preparation as claimed in any preceding claim wherein the enhancer is or includes sodium cholate.
12. A preparation as claimed in any preceding claim wherein the enhancer is or includes sodium deoxycholate.
10
13. A preparation as claimed in any preceding claim wherein the absorption enhancer is or includes a non-ionic surfactant.
14. A preparation as claimed in claim 13 wherein the absorption enhancer is a polyoxy-ethyleneglyceroltriricinoleat derivative.
15
15. A preparation as claimed in claim 14 wherein the absorption enhancer is Cremophor EL.
16. A preparation as claimed in any preceding claim wherein the enhancer is or includes a cyclodextrin or its derivatives.
20
17. A preparation as claimed in claim 16 wherein the enhancer is a hydroxypropylbeta-cyclodextrin.
18. A preparation as claimed in any preceding claim wherein the calcitonin is salmon calcitonin.
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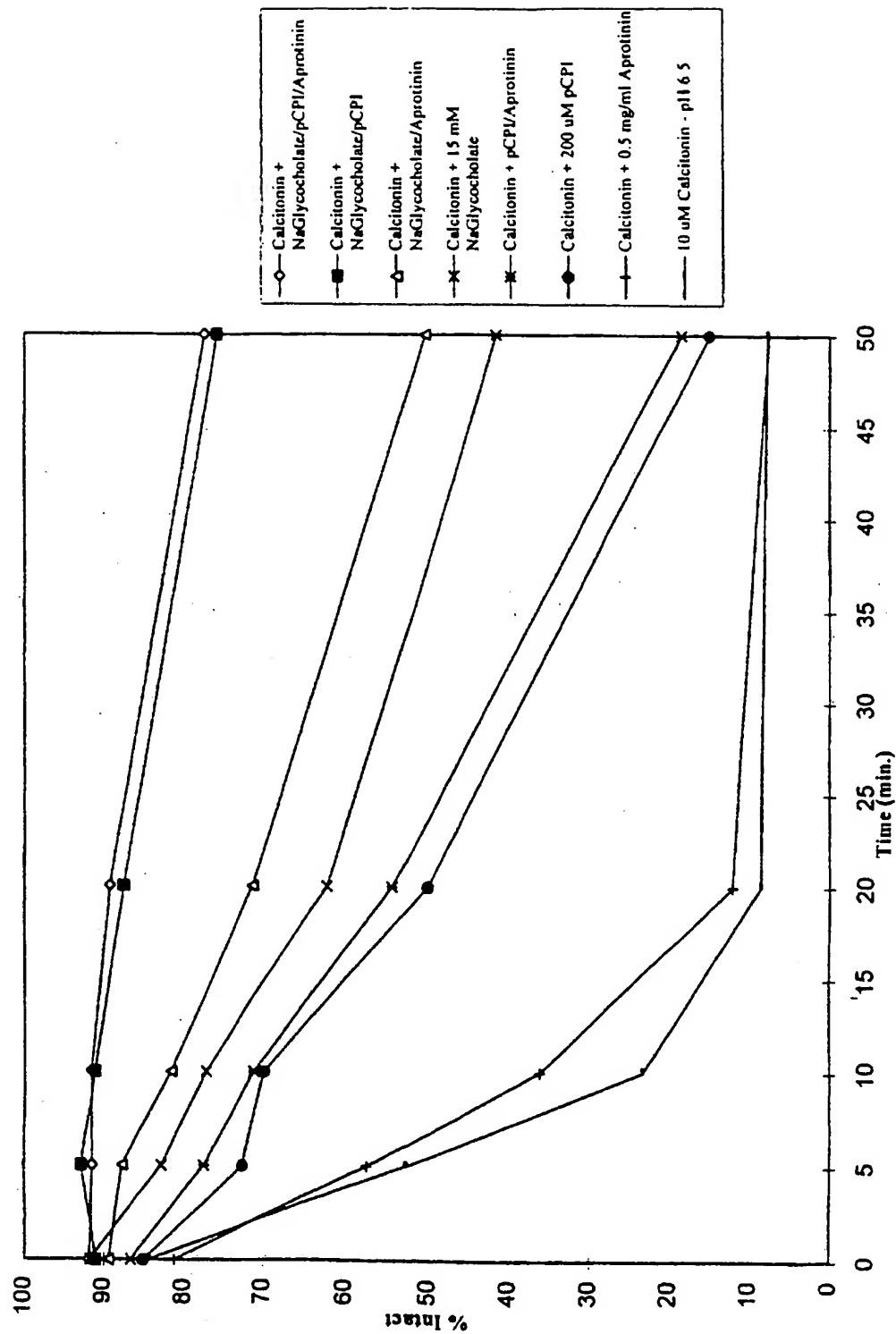
19. A preparation as claimed in any of claims 1 to 17 wherein the calcitonin is human calcitonin.
20. An oral calcitonin preparation comprising:-
- 5 a calcitonin, preferably salmon calcitonin or human calcitonin,
- sodium glycocholate, sodium cholate or sodium deoxycholate and
- potato carboxypeptidase .
- 10 21. An oral calcitonin preparation substantially as hereinbefore described with reference to the Examples.
22. An oral calcitonin preparation as claimed in any preceding claim in a liquid form.
- 15 23. An oral calcitonin preparation as claimed in any of claims 1 to 21 in a solid form, preferably incorporated in a tablet or capsule.
24. An oral calcitonin preparation substantially as hereinbefore described.
- 20 25. A pharmaceutical composition for oral administration of a calcitonin comprising an oral preparation as claimed in any preceding claim.
26. A pharmaceutical composition as claimed in claim 25 in the form of a tablet or capsule having an enteric coating.

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27. A pharmaceutical composition as claimed in claim 25 or 26 wherein the composition includes stabilising agent(s) and/or lyoprotectant(s).
- 5 28. A pharmaceutical composition as claimed in claim 27 wherein the lyoprotectant(s) is selected from a polyethylene glycol, sugars including glucose, lactose, trehalose, and/or mannitol.
- 10 29. A pharmaceutical composition as claimed in any of claims 25 to 28 wherein the composition includes pH regulator(s).
30. A pharmaceutical composition as claimed in claim 29 wherein the pH regulator(s) is prepared from organic acids such as citric or tartaric or succinic acids and/or their salts either alone or in combination.
- 15 31. A pharmaceutical composition substantially as hereinbefore described.

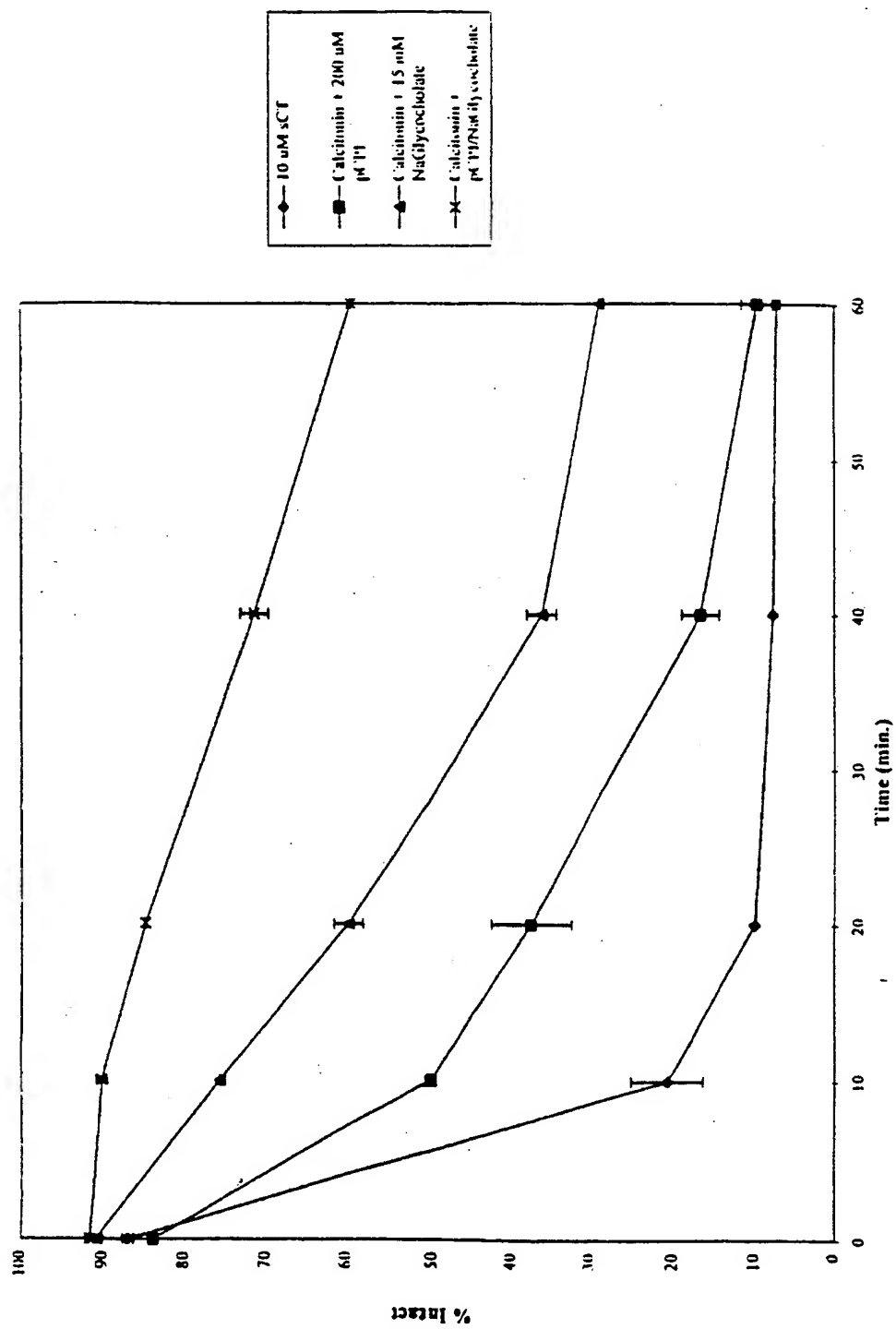
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Figure 1 - Effect of protease inhibitors on sCT stability in rat intestinal mucosal homogenate pH 6.5



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Figure 2 - Effect of protease inhibitors on sCT stability in rat intestinal mucosal homogenate pH 7.4



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Figure 3 - Effect of formulation on stability of sCT in upper intestinal homogenate. Comparison of bile salts

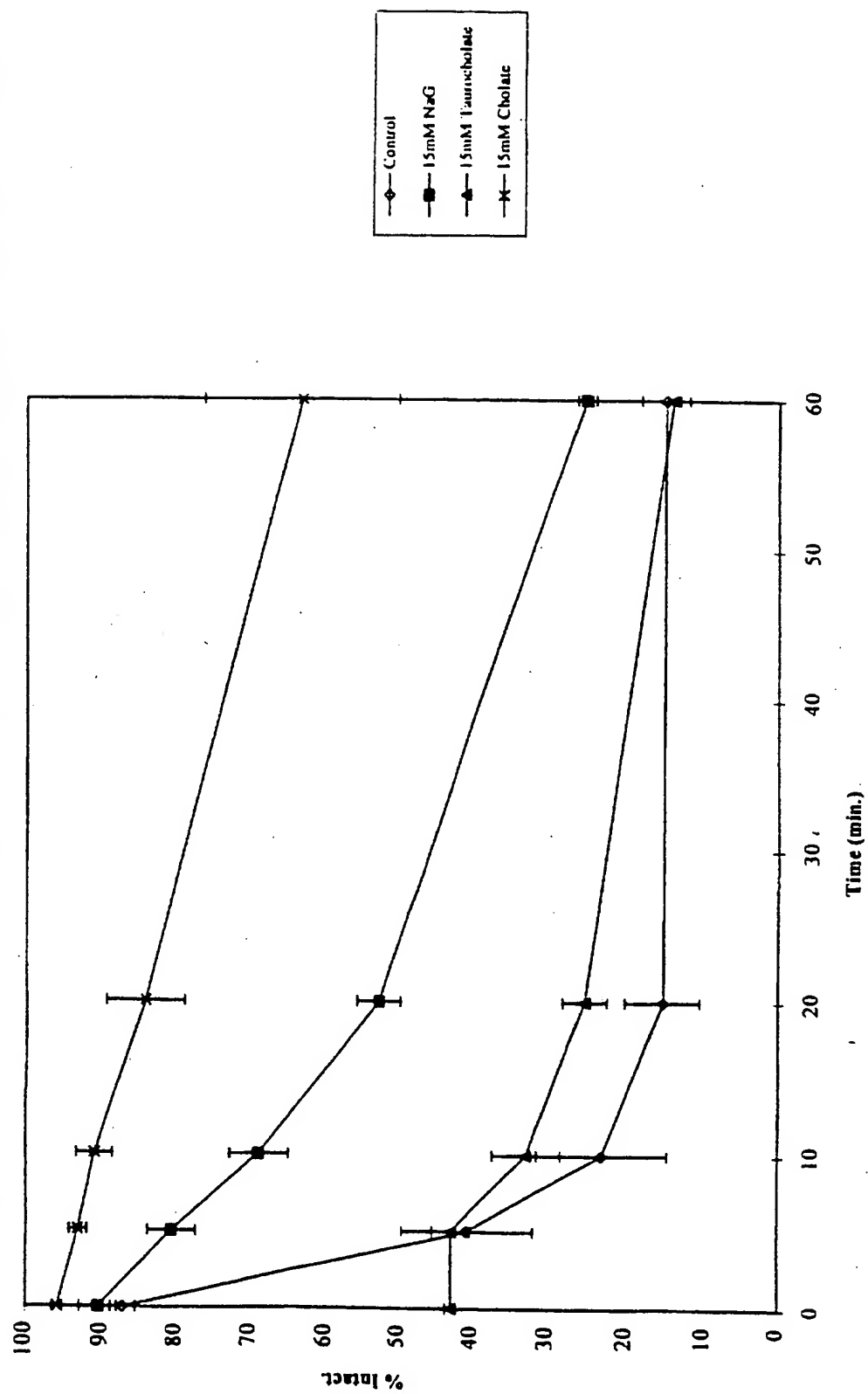
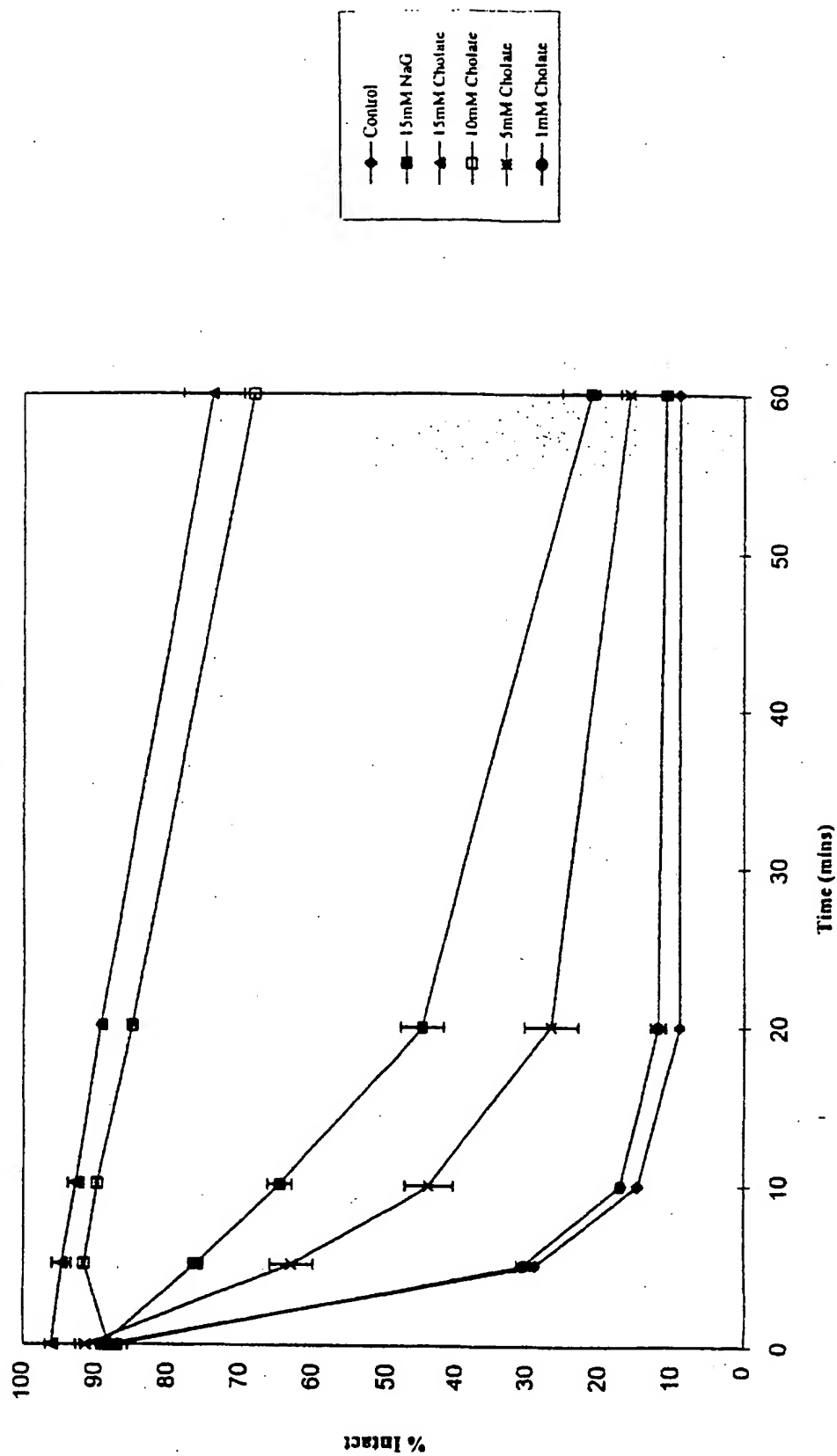
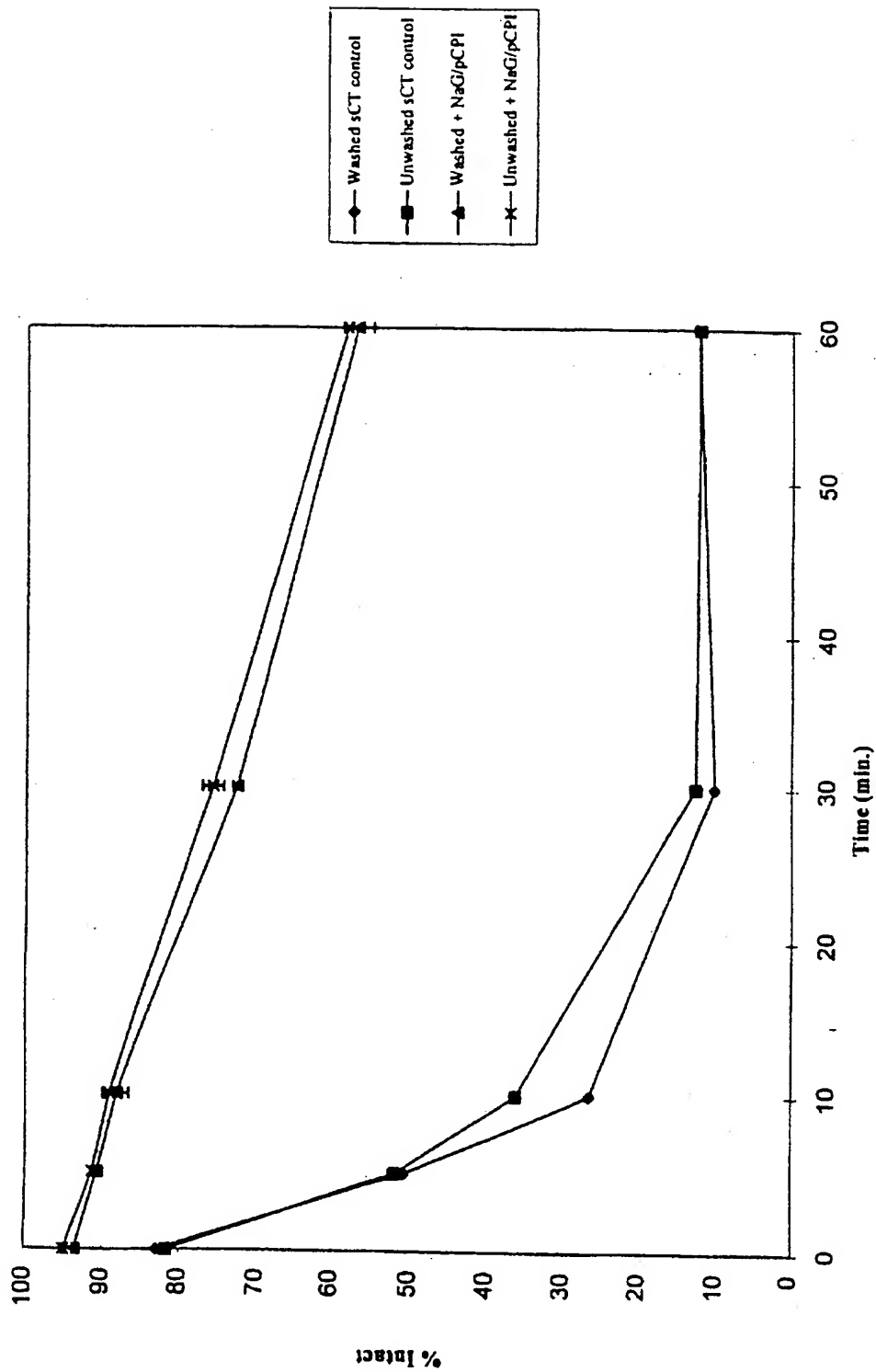


Figure 4 - Effect of formulation on the stability of sCT in upper intestinal mucosal homogenate. NaCholate dose/response curve



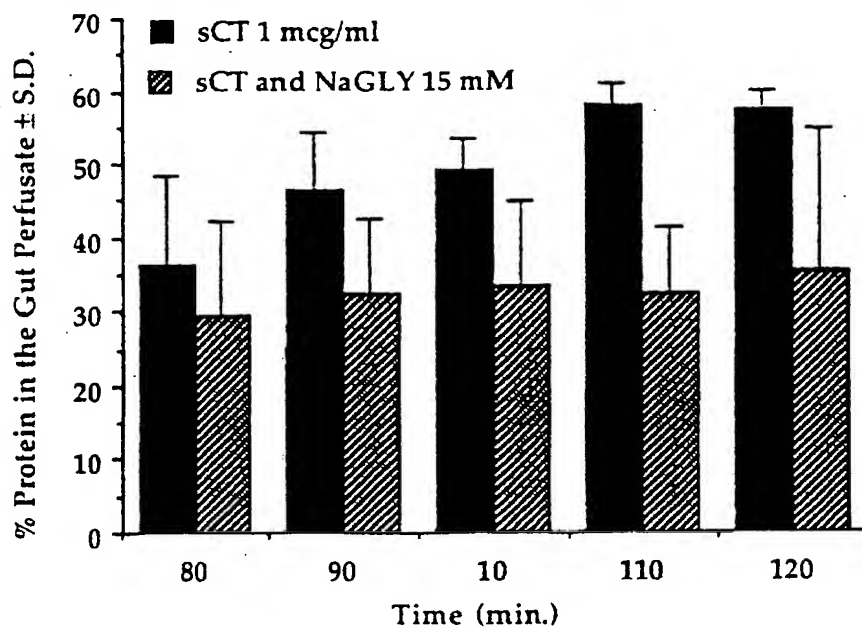
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Figure 5 - Effect of formulation on sCT stability in lower intestinal (terminal ileum) mucosal homogenate.



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Figure 6 The effect of excipient on sCT concentration in the rat gut perfusate



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Figure 7 - Effect of excipients NaG and pCPI on rat plasma calcium during perfusion of 1.0 ug/ml sCT.

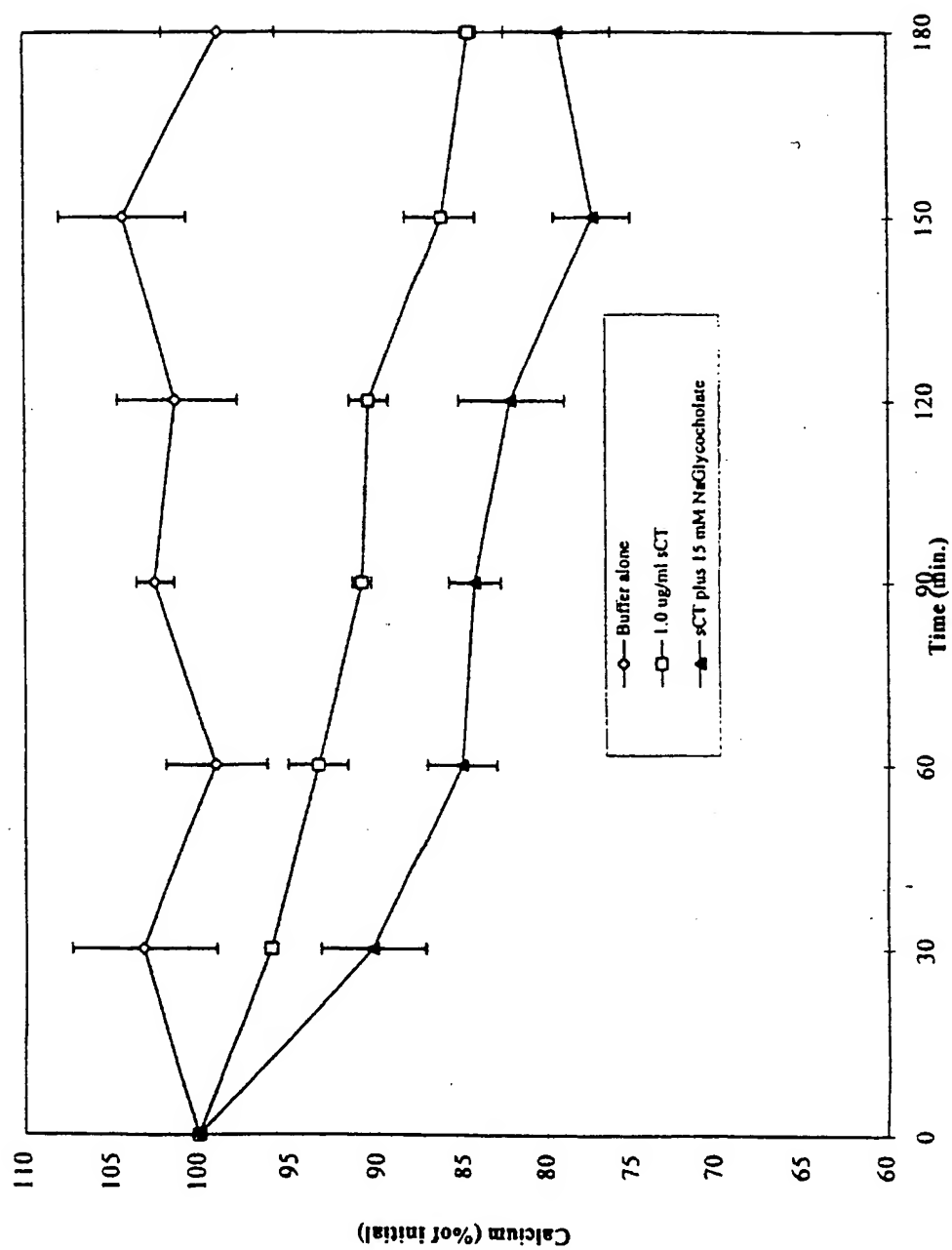


Figure 8 - Effect of sCT concentration on the pharmacodynamic response

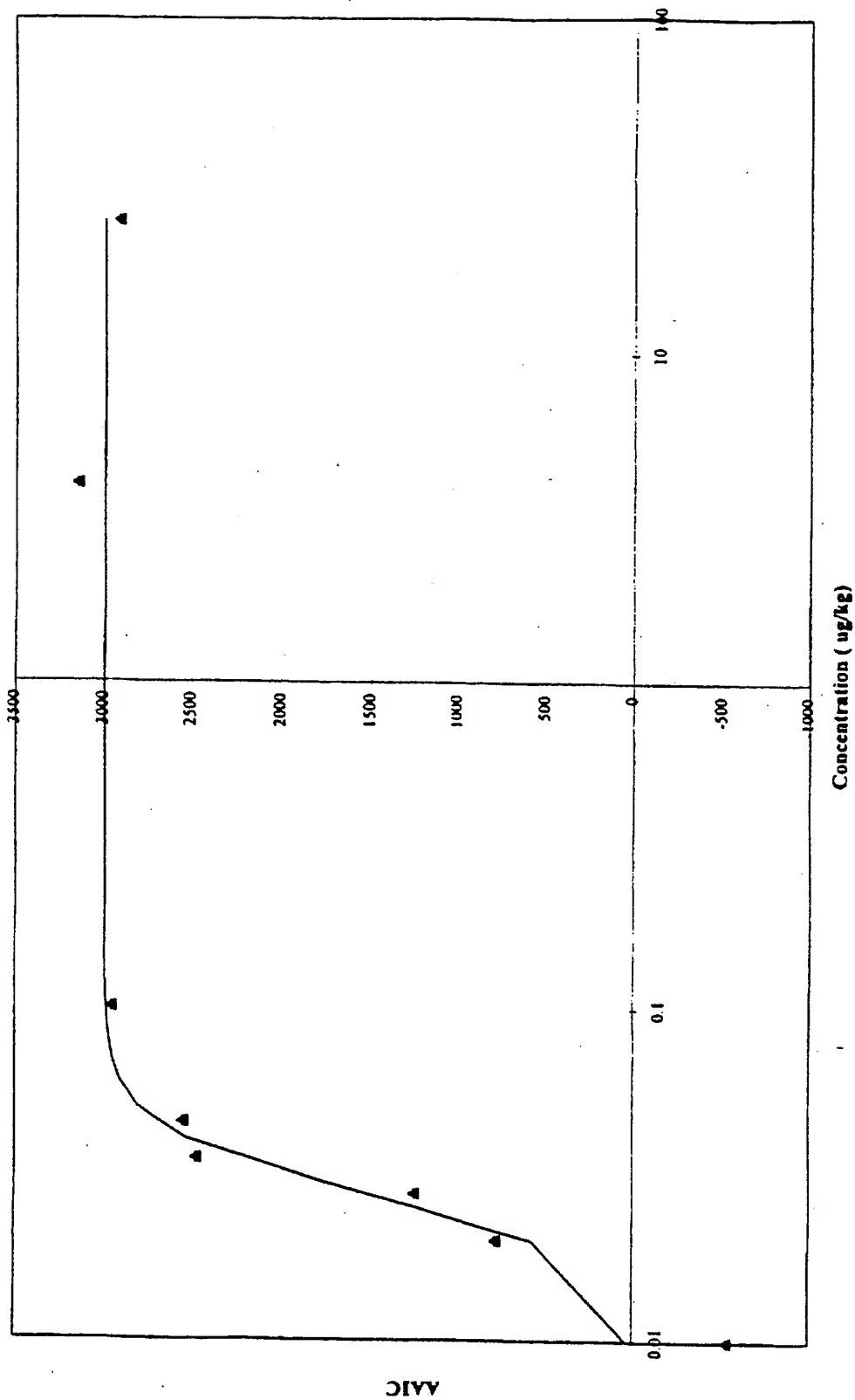
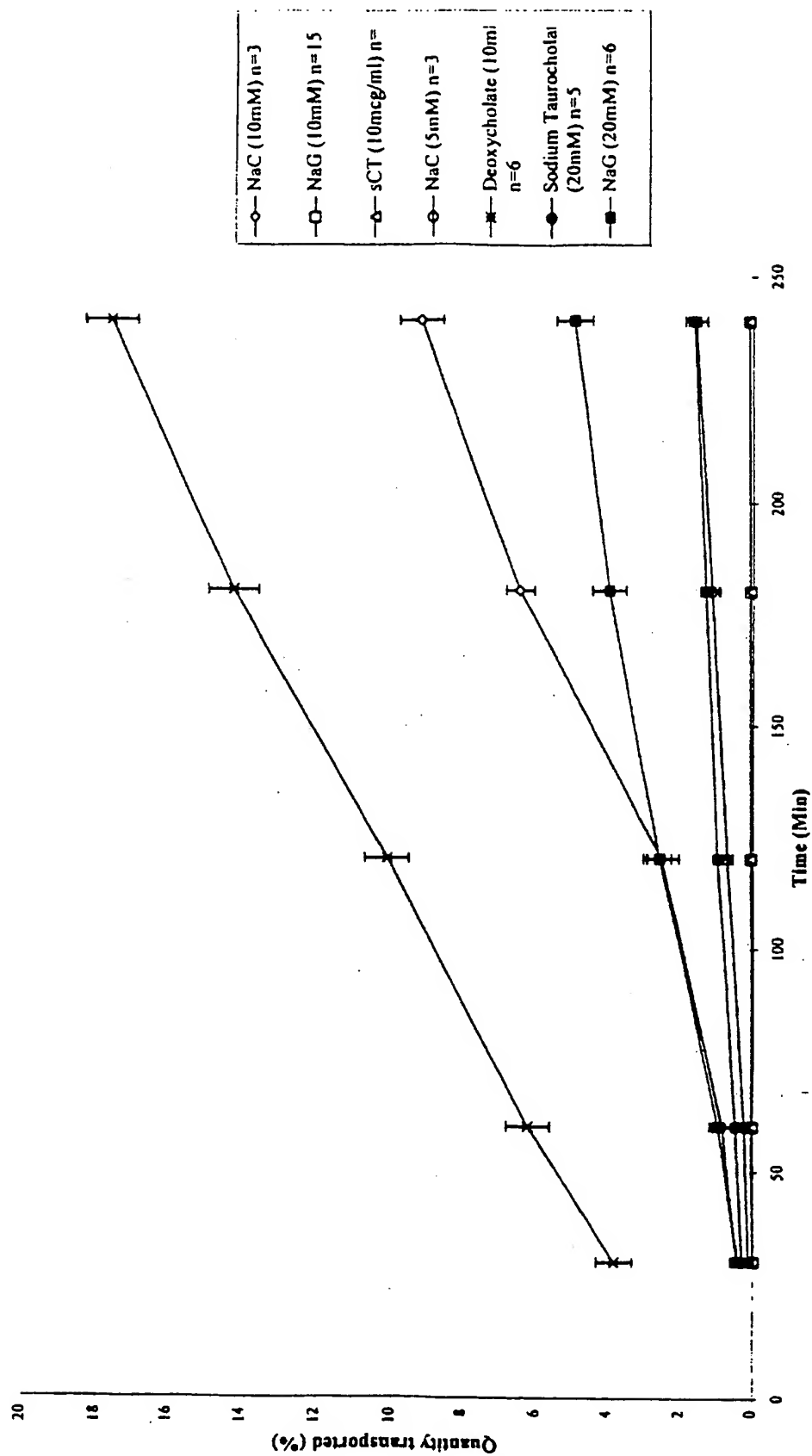
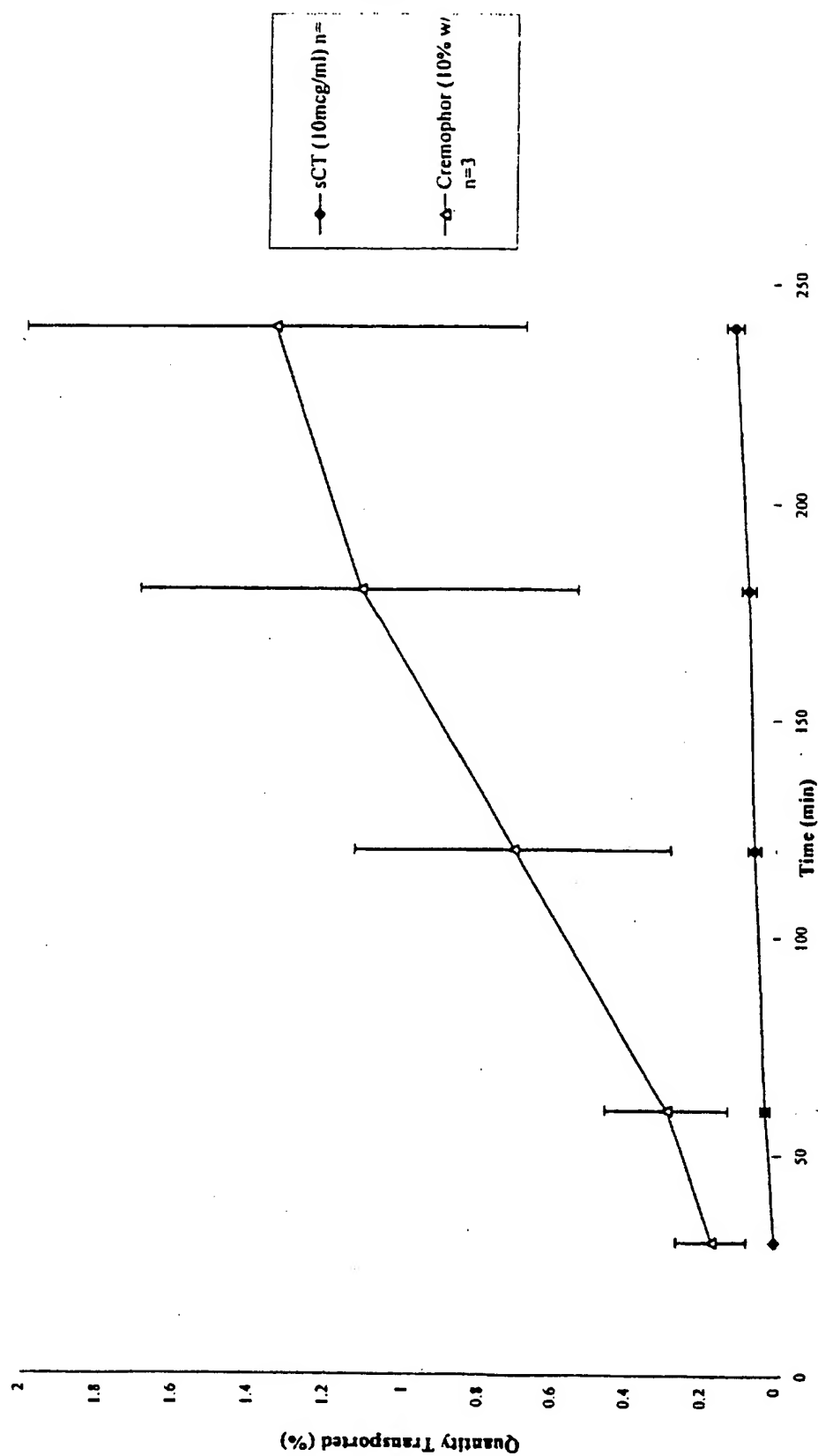


Figure 9 : The Effect of Bile salts on the transport of sCT across the CaCo II Monolayer



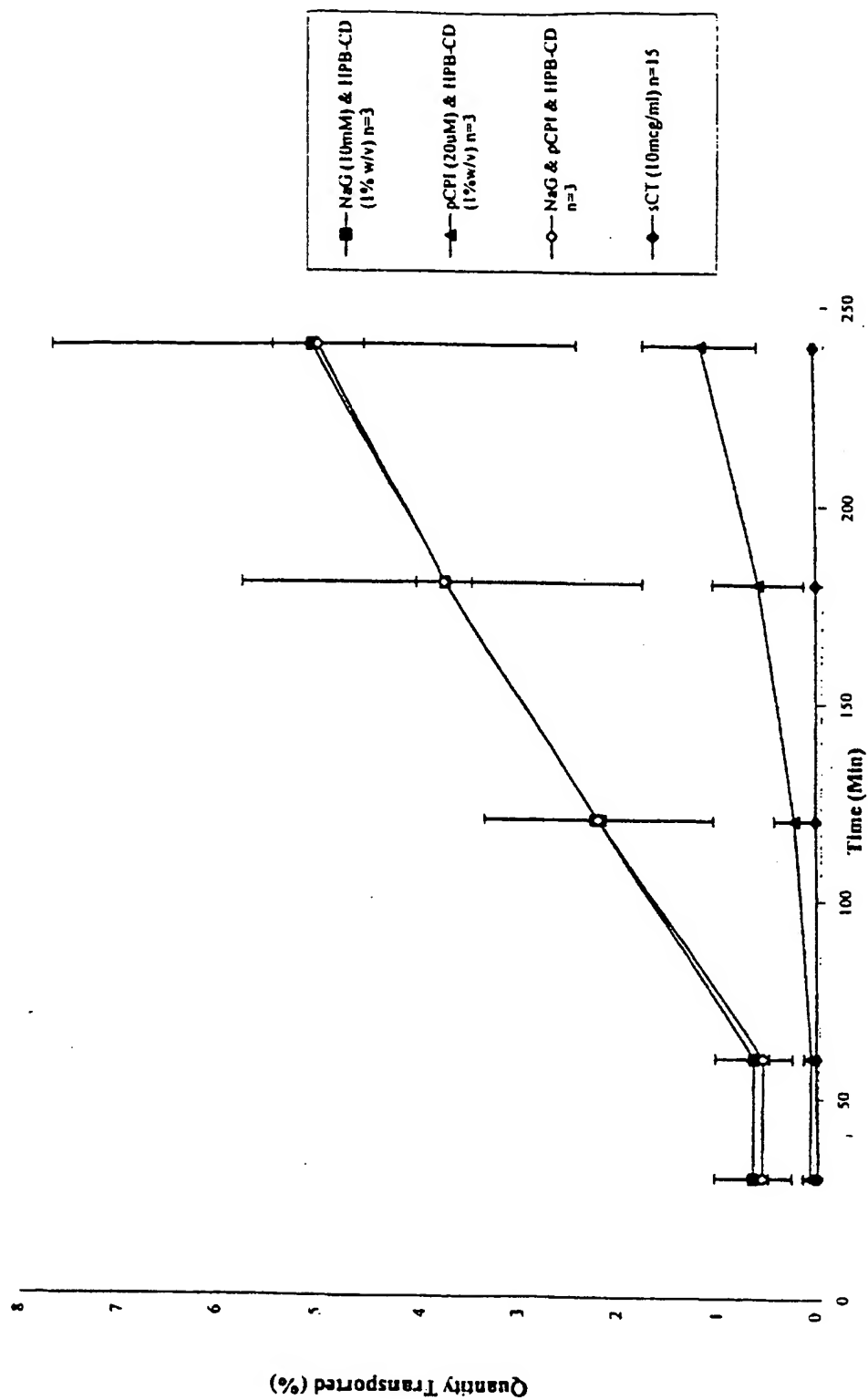
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Figure 10 : The Effect of Cremophor on the Transport of sCT across the CaCo II Monolayer.



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Figure 11 : The Effect of Formulation excipients in Combination with Hydroxypropyl B-CD on the Transport of sCT across the CaCo II Monolayer



INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/IE 96/00086

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/23 A61K47/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 06854 A (SMITH-KLINE BEECHAM FARMACEUTICI S.P.A) 15 April 1993 see page 2, line 1 - line 18; claims 1-9; examples 37-40	1,2, 18-31
Y	see page 4, line 8 - line 18 see page 10, line 12 - page 11, line 11 see page 12, line 20 - line 32	3-17
Y	--- EP 0 127 535 A (HADASSAH MEDICAL ORGANIZATION) 5 December 1984 see page 3, line 21 - line 36; claims; examples 1,20,21 see page 6, line 1 - line 10 see page 7, line 1 - line 6 --- -/--	3-12,16, 17

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☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 07472 A (PFIZER INC.) 14 April 1994 see page 3, line 10 - line 11; claims see page 5, line 27 - line 28 see page 7, line 3 ---	13-15
X	GB 2 257 908 A (SANDOZ LTD.) 27 January 1993 see page 3, line 5 - page 5, line 12; claims; examples 1,2 see page 7, paragraph 5 - page 9, paragraph 2 -----	1,6-12, 18,19, 21-31

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No

PCT/IE 96/00086

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9306854 A	15-04-93	IT 1251685 B	19-05-95
		AU 2683492 A	03-05-93
		BR 9206707 A	31-10-95
		CA 2120755 A	15-04-93
		EP 0607229 A	27-07-94
		JP 7500099 T	05-01-95
		PT 100946 A	29-10-93

EP 127535 A	05-12-84	CA 1223200 A	23-06-87
		JP 6078238 B	05-10-94
		JP 60069028 A	19-04-85
		US 4579730 A	01-04-86

WO 9407472 A	14-04-94	AU 5095393 A	26-04-94
		CA 2145763 A	14-04-94
		EP 0662826 A	19-07-95
		FI 934317 A	03-04-94
		HU 69400 A	28-09-95
		JP 7507565 T	24-08-95
		NO 951265 A	31-05-95
		ZA 9307268 A	30-03-95

GB 2257908 A	27-01-93	BE 1007752 A	17-10-95
		CH 685600 A	31-08-95
		DE 4222647 A	21-01-93
		FR 2682598 A	23-04-93
		IT 1263222 B	05-08-96
		JP 5194260 A	03-08-93
